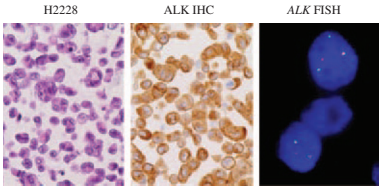
## IN THIS ISSUE

- **Heterogeneity of Anaplastic Lymphoma Kinase Gene Rearrangement in Non-Small-Cell Lung Carcinomas: A Comparative Study Between Small Biopsy and Excision Samples**




The authors set out to evaluate the heterogeneity of anaplastic lymphoma kinase (ALK) rearrangement in non-small cell lung cancer (NSCLC) excision samples using fluorescent *in situ* hybridization (FISH), and compare the FISH score of *ALK* rearrangement in excision and small biopsy specimens from the same patient. *ALK* FISH-positivity was analyzed in 20 *ALK* IHC-positive patients, of which 6 were given crizotinib treatment. Observation areas (6–10) were determined in each excision specimen, and the number of *ALK* FISH-positive areas (≥15% rearrangement detected) was assessed for evaluation of heterogeneity of *ALK* rearrangement. In small biopsy specimens, *ALK* FISH score was defined as positive (≥15% rearrangement detected), equivocal (5% to 14% rearrangement detected), or negative (<4% rearrangement detected). The results showed that *ALK* rearrangement was found in 50 out of 64 observation areas (81.8%) in 9 excision specimens. *ALK* FISH-positivity was observed in 100% of excision specimens (6/6) while it was only detected in 50% (3/6) of the small biopsy specimens of the same patients; 33% of these samples were equivocal (2/6, from patients responded to crizotinib), and 17% were negative (1/6). Taken together, the findings demonstrated *ALK* rearrangement heterogeneity in NSCLC specimens using FISH, and suggested that IHC-positive/FISH-equivocal cases in small biopsy specimens should not be considered as true *ALK* "false negatives". (p. 800)

- **Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC**

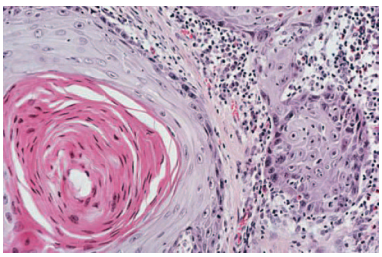
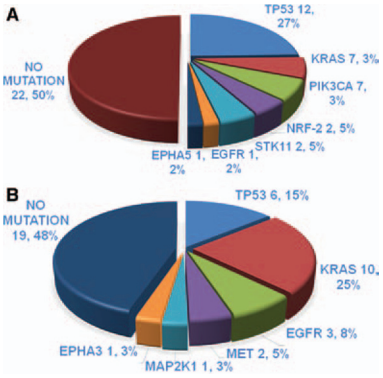


Image source: NCI

In this study, the authors assessed the overall survival (OS) and patterns of tumor recurrence in 340 patients with stage I non-small cell lung cancer (NSCLC), who received surgery or stereotactic ablative radiotherapy (SABR). They retrospectively analyzed clinical data from patients with fluoro-deoxyglucose positron emission tomography/computed tomography-staged NSCLC treated with surgery (n=143) or SABR (n=197) at the University Medical Center Groningen, Netherlands (2007–2010). Patients were 10 years younger, with better WHO performance and less comorbidities, in the group treated with surgery versus that with SABR. Between the SABR arm and the surgery arm, there was no difference in OS (adjusted hazard ratio [HR] 1.07; $p$=0.73), local control (adjusted sub-HR 1.21; $p$=0.75) and distant recurrences (adjusted sub-HR 1.01; $p$=0.97). However, significantly higher locoregional recurrences were observed in the SABR arm versus the surgery arm (adjusted sub-HR 2.51; $p$=0.028). Independent predictive factors for OS were nodal failure (HR 2.16) and distant metastases (HR 2.12), but not local failure (HR 1.00). The authors concluded that although adjusted OS was similar between patients with stage I NSCLC treated with surgery and SABR, the SABR group had worse locoregional tumor control as a result of more nodal failures versus surgery. The findings underscored the importance of improving mediastinal and hilar staging for optimal treatment decisions. (p. 826)

- **Diagnostic Mutation Profiling and Validation of Non–Small-Cell Lung Cancer Small Biopsy Samples using a High Throughput Platform**

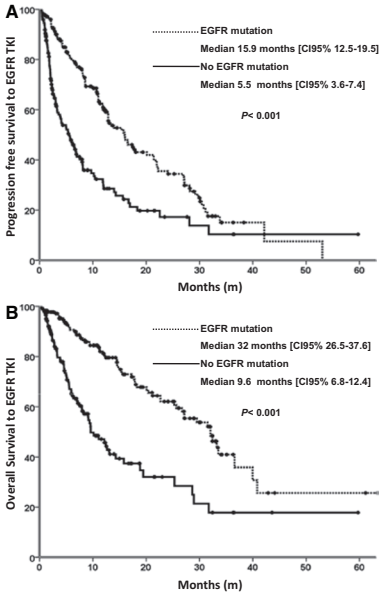



The aim of this study was to evaluate the mass spectrometry-based Sequenom LungCarta panel and MassARRAY platform using DNA extracted from a single 5 μM formalin-fixed paraffin-embedded non-small cell lung cancer (NSCLC) tissue section for diagnostic mutation profiling. Ninety NSCLC samples, consisting of 72 lung biopsies, 13 metastatic tissue biopsies, 3 resections, and 2 cytology samples, were analyzed for mutations and were subsequently validated by a combination of molecular techniques. The Sequenom assay detected 55 mutations in *TP53* (22), *KRAS* (15), *EGFR* (5), *MET* (3), *PIK3CA* (3), *STK11* (2), *NRF-2* (2), *EPHA5* (1), *EPHA3* (1), and *MAP2K1* (1) in 52% of the samples tested. They found that next-generation sequencing (NGS) detected 7 additional *TP53* mutations but NGS used more tumor sections of greater thickness (5 × 10 μM) versus that for the Sequenom assay (1 × 5 μM). The authors concluded that the Sequenom Lung Carta panel is a clinically useful diagnostic screening test for small biopsy samples of NSCLC. This assay is capable of screening 214 mutations across 26 genes, and confidently detects mutations at neoplastic cell content levels of 10% and above from a single 5 μM section. (p. 784)

- **Updated Frequency of EGFR and KRAS Mutations in NonSmall-Cell Lung Cancer in Latin America: The Latin-American Consortium for the Investigation of Lung Cancer**

This report provided an update on the distribution of epidermal growth factor receptor (*EGFR*) and *KRAS* mutations in Latin American patients with non-small cell lung cancer (NSCLC). In previous studies, 40% Asian and 15% Caucasian were found to harbor the *EGFR* mutations. The present study included 5738 NSCLC samples from Argentina (1713), Mexico (1417), Colombia (1939), Peru (393), Panama (174), and Costa Rica (102). The study population consists of patients with median age of 62.2 ± 12.3 years, 53.5% women, 46.7% with a history of smoking, and 95.2% with adenocarcinoma. *EGFR* mutations were found in 26.0% of the overall study population, with 14.4% from Argentina, 34.3% from Mexico, 24.7% from Columbia, 51.1% from Peru, 27.3% from Panama, and 31.4% from Costa Rica. *KRAS* mutations were detected in 14.0% of the overall population. The *EGFR* mutations in patients with adenocarcinoma were independently correlated with female, nonsmoker status, mestizo/indigenous ethnicity, and the absence of *KRAS* mutation (all $p<0.001$). Patients treated with EGFR inhibitors demonstrated an overall response rate of 60.6%, a median progression-free survival of 15.9 months, and overall survival of 32 months. Taken together, the findings confirmed that the frequency of *EGFR* mutations in Latin America is intermediate between that in the Asian and Caucasian populations, and also supported the genetic heterogeneity of NSCLC around the world. (p. 838)

- **Lung Cancer Workshop XI: *Tobacco-Induced Disease: Advances in Policy, Early Detection and Management***




The special article covers the Prevent Cancer Foundation Lung Cancer Workshop XI: Tobacco-Induced Disease: Advances in Policy, Early Detection and Management held in New York, NY in 2014. The steering committee consists of technical experts David Yankelevitz, Thomas Baer, Rick Avila, Carolyn Aldigé of the Prevent Cancer Foundation, and Laurie Fenton Ambrose of the Lung Cancer Alliance. The two goals of the Workshop were to improve quantitative imaging for management of early lung cancer through innovative research on its use to assess new treatments, and to review progress of the application of quantitative imaging for lung cancer and other tobacco-induced diseases including coronary artery disease and chronic obstructive pulmonary disease. The central focus of the Workshop was on the issues regarding the national implementation of high quality low-dose computed tomography (LDCT). Efforts in accelerating progress in the integration of quantitative imaging into early lung cancer have been largely successful as a result of collaborations with professional organizations, including the Radiological Society of North America and the formation of Quantitative Imaging Biomarker Alliance. Included in the discussion were methodologies issues with quantitative imaging, the impact of screening management on quantitative imaging, the status of harms reduction (dose minimization), the precision of current lung cancer screening quantitation, future advances on evaluation of other thoracic structures while screening, and other applications in lung cancer management. The cost-benefit analysis of LDCT estimated $25,000 per life-year saved, comparable to mammography and cervical cancer screening, and similar to colorectal screening. Important actions relative to health policy in the national implementation of lung cancer screening were recommended: firstly, to request Centers for Medicare and Medicaid Services for full reimbursement coverage of LDCT screening at a national level; secondly, to support the Department of Defense and its Healthy Base Initiative; and finally, to commission a study by the Institute of Medicine of the National Academy of Sciences on imaging research as it relates to lung and heart diseases. (p. 762)

## RESEARCH WATCH

- **Overall Response Rate, Progression-Free Survival, and Overall Survival With Targeted and Standard Therapies in Advanced Non–Small-Cell Lung Cancer: A US Food and Drug Administration Trial-Level and Patient-Level Analyses**

The US FDA conducted an analysis of 14 randomized, active-controlled trials of treatments involving 12,567 patients with advanced non-small cell lung cancer (NSCLC) to elucidate the relationships between overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) at trial and patient levels. Experimental treatments in the trials included crizotinib, afatinib, erlotinib, nab-paclitaxel plus carboplatin, vandetanib, cetuximab, gefitinib, bevacizumab, pemetrexed plus cisplatin, and pemetrexed alone. Two trials assessed targeted therapies in *EGFR* mutation-positive population and one trial in *ALK*-positive population. At the trial level, strong association between ORR and PFS was observed ($R^2 = 0.89$), but not between ORR and OS ($R^2 = 0.09$), and between OS and PFS ($R^2 = 0.08$). At the patient level, ORR was significantly associated with improved PFS (hazard ratio [HR] 0.40) and OS (HR 0.40), when compared with non-responders. To conclude, the lack of correlation between ORR and OS, and between OS and PFS at the trial level was likely a result of cross-over and longer survival after progression in trials of targeted therapies and first-line treatments. ORR and PFS was strongly associated at trial and patient levels, indicating a dramatic effect on ORR from a therapy in advanced NSCLC may have a large effect on PFS.

Blumenthal GM, Karuri SW, Zhang H, et al. Overall Response Rate, Progression-Free Survival, and Overall Survival With Targeted and Standard Therapies in Advanced Non-Small-Cell Lung Cancer: A US Food and Drug Administration Trial-Level and Patient-Level Analyses. *J Clin Oncol*, doi:10.1200/jco.2014.59.0489 (2015).

- **Association of *EGFR* L858R Mutation in Circulating Free DNA With Survival in the EURTAC Trial**

The prespecified analysis of the EURTAC trial (2007–2011) aimed to evaluate the use of circulating free DNA (cfDNA) from blood samples as a surrogate for tumor biopsy to determine the association of *EGFR* mutations in cfDNA with outcome in patients with advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutations. Patients had no prior chemotherapy for metastatic disease, and were treated with erlotinib or chemotherapy in the EURTAC study. Using a novel peptide nucleic acid–mediated 5´ nuclease real-time polymerase chain reaction (TaqMan) assay, *EGFR* mutations were detected in cfDNA from 76 of 97 blood samples (78%). Shorter median overall survival (OS) was found in patients harboring L858R mutation versus exon 19 deletion in cfDNA (13.7 vs. 30.0 months; $P<0.001$). According to univariate analysis, L858R mutation in tumor tissue or cfDNA predicts worse OS (hazard ratio [HR] 2.70; $P<0.001$) and progression-free survival (PFS) (hazard ratio [HR] 2.04; $P=0.008$). Patients with L858R mutation in both tumor tissue and cfDNA had a median OS of 13.7 months while those with the mutation in tumor tissue but not cfDNA had a median OS of 27.7 months (HR 2.22; $P=0.03$). Erlotinib therapy was the sole independent predictor of prolonged PFS in the multivariate analysis of patients with *EGFR* mutations in cfDNA (HR 0.41; $P=0.003$). Taken together, L858R mutation in cfDNA is associated with poorer survival; the assay used in this study could efficiently evaluate these mutations in cfDNA, which could be a novel surrogate prognostic marker in the study population.

Karachaliou N, Mayo-de las Casas C, Queralt C, et al. Association of egfr l858r mutation in circulating free dna with survival in the eurtac trial. *JAMA Oncology*, doi:10.1001/jamaoncol.2014.257 (2015).

- **Crizotinib Therapy for Advanced Lung Adenocarcinoma and a *ROS1* Rearrangement: Results From the EUROS1 Cohort**

The authors conducted a retrospective study of crizotinib treatment in 32 European patients with stage IV lung adenocarcinoma, harboring *ROS1* rearrangement as shown by fluorescent *in situ* hybridization. The study population had a median age of 50.5 years, 64.5% women and 67.7% never-smokers. Of the 29 patients evaluable for best response, 4 had disease progression, 2 had stable disease, and 24 had objective response, which included 5 complete responses (overall response rate: 80%; disease control rate: 86.7%). Among the 30 patients evaluable for progression-free survival (PFS), a median PFS of 9.1 months and a PFS rate of 44% at 12 months were achieved, with no unexpected side effects. Among the 26 patients who were treated with pemetrexed alone or in combination with platinum, before or after the crizotinib treatment, a response rate of 57.7% and a median PFS of 7.2 months were achieved. The findings indicated substantial activity of crizotinib in patients with advanced lung adenocarcinoma harboring a *ROS1* rearrangement, supporting screening lung cancer patients for *ROS1* for the treatment with crizotinib or other ROS1 inhibitors.

Mazieres J, Zalcman G, Crino L, et al. Crizotinib Therapy for Advanced Lung Adenocarcinoma and a ROS1 Rearrangement: Results From the EUROS1 Cohort. *J Clin Oncol*, doi:10.1200/jco.2014.58.3302 (2015).

- **Causation of Cigarette Smoke–Induced Emphysema by p-Benzoquinone and Its Prevention by Vitamin C**

The authors set out to show the cause of pathogenesis of lung injury in emphysema, and discovered that p-benzoquinone (p-BQ) released after cigarette smoke (CS) exposure in the lungs of the guinea pigs contributed to the damage of alveolar cells leading to emphysema. They also demonstrated that the condition could be prevented by vitamin C. Guinea pigs were vitamin C-restricted and subjected to whole-body CS exposure from Kentucky research cigarettes (3R4F) per day or intramuscular injection of similar amount p-BQ to that released in CS-exposed lungs with and without oral supplementation of vitamin C. The results showed progressive accumulation of p-BQ in the lung, in conjunction with damage of alveolar cells and emphysema, following progressive exposure to CS or p-BQ. Arylation, oxidative stress, inflammation, and apoptosis were observed. The p-BQ accumulation in the lung and the pathogenesis of emphysema was shown to be prevented by 30 mg/kg body weight/d of vitamin C, which could be an antagonist of p-BQ. Taken together, the evidence suggested that inactivation of p-BQ via a moderately high dose of vitamin C could prevent the development of emphysema in chronic smokers.

Ghosh A, Ganguly S, Dey N, et al. Causation of Cigarette Smoke–Induced Emphysema by p-Benzoquinone and Its Prevention by Vitamin C. *American journal of respiratory cell and molecular biology* 52, 315–322, doi:10.1165/rcmb.2013-0545OC (2014).

- **Gender Equality and Smoking: A Theory-Driven Approach to Smoking Gender Differences in Spain**

This study investigated the relationship of changes in gender equality and variation in smoking prevalence stratified by gender, education and birth cohort in Spain from representative National Health Surveys (1960 to 2010). The Gender Inequality Index (GII) was measured in 5-year intervals, ranging from 0 to 1 (1 being the highest inequality), and covered reproductive health, empowerment and labor market. The findings showed a decline in GII in Spain from 0.65 to 0.09 over the past 5 decades, which was inversely correlated to an increasing female-male smoking ratio. Compared with men, similar smoking prevalences were observed in the youngest birth cohort of the study (born 1980–1990) and highly educated women. Also, the first to show a decline in smoking prevalence were highly educated women versus those less educated. The authors concluded that the dramatic drop in gender inequality in Spain over the past 5 decades coincided with converging trends in smoking prevalence for men and women. Wide variation in patterns of smoking prevalence by birth cohort and education levels was observed. They recommended gender-sensitive measures in tobacco control and policies in countries at the beginning of the tobacco epidemic.

Bilal U, Beltran P, Fernandez E, Navas-Acien A, Bolumar F, Franco M. Gender equality and smoking: a theory-driven approach to smoking gender differences in Spain. *Tobacco control*, doi:10.1136/tobaccocontrol-2014–051892 (2015).

- **The Use of Legal, Illegal and Roll-Your-Own Cigarettes to Increasing Tobacco Excise Taxes and Comprehensive Tobacco Control Policies: Findings from the ITC Uruguay Survey**

This study analyzed whether smokers switch to manufactured illegal or roll-your-own (RYO) cigarettes as a result of a change in their relative price in Uruguay after adjusting for covariates, such as sociodemographic characteristics, smokers' exposure to antismoking messaging, health warning labels and tobacco marketing. The results demonstrated a 10% increase in the relative price ratio of legal to RYO cigarettes correlating with a 4.6% increase in the switch from manufactured legal cigarettes to RYO cigarettes ($p \leq 0.05$). Lower odds of switching from manufactured legal cigarettes to RYO were associated with increased exposure to antismoking messaging ($p \leq 0.05$). There was no significant association between the manufactured illegal to legal cigarette price ratios and switching to manufactured illegal cigarettes from legal ones, indicating a rise in prices of legal cigarettes does not trigger smokers to switch to manufactured illegal ones. To conclude, the authors urged policymakers to narrow price variability in the tobacco market in an attempt to enhance the effectiveness in smoking reduction through increased taxes and prices. Additionally, reducing the switch to cheaper RYO cigarettes by boosting antismoking messaging could lower tax avoidance in Uruguay.

Curti D, Shang C, Ridgeway W, Chaloupka FJ, Fong GT. The use of legal, illegal and roll-your-own cigarettes to increasing tobacco excise taxes and comprehensive tobacco control policies: findings from the ITC Uruguay survey. *Tobacco control*, doi:10.1136/tobaccocontrol-2014–051890 (2015).

## NEWS IN BRIEF

- **CMS: National Coverage Determination for Low-Dose Computed Tomography Screening for Lung Cancer**

Image source: FDA

Medicare will now cover low-dose computed tomography (LDCT) screening for lung cancer once per year for Medicare beneficiaries who are 55–77 years of age, current smokers or those who have quit smoking within the last 15 years, have at least 30 pack-years of smoking history, and obtained a written order from a physician or qualified non-physician practitioner. The coverage includes a visit for counseling and shared decision-making on the risks and benefits of lung cancer screening. The national coverage determination also includes required data collection and specific criteria for coverage eligibility for radiologists and imaging centers.

- **Chemotherapy Trials for Advanced Cancers of the Lung and Pancreas Overestimate Survival for Elderly Medicare Patients**

Image source: NCI

Lamont et al. reported in the *Journal of National Cancer Institute* that clinical trial results assessing chemotherapy for advanced pancreatic and lung cancers demonstrated a tendency of correct estimation of survival for Medicare patients aged 65–74 years, but overestimation of survival in older Medicare patients by 6–8 weeks. The authors analyzed Surveillance, Epidemiology, and End Results Program (SEER)–Medicare data of 14,097 advanced pancreatic or lung cancer patients aged 65 or older, treated with one of three recommended first-line chemotherapies. Their survival data were compared with that of clinical trial patients (n=937) of the same diagnosis and disease stage but without age restrictions. Comparing elderly Medicare patients with clinical trial patients, the survival times in stage IV non-small cell lung cancer were 7.3 versus 8.9 months ($P = 0.91$) treated with carboplatin and paclitaxel, and 8.2 versus 10.2 months ($P \leq 0.01$) in extensive small cell lung cancer treated with cisplatin/etoposide. Younger Medicare patients had similar survival times to clinical trial patients, indicating that choice of usual-care treatment by physicians for this group has been reasonable. The findings underscored the need to take into account of the various factors like functional status, comorbidity and general health status in comprehensive geriatric assessments, leading to better patient stratification for treatments.

- **FDA Grants Orphan Drug Designation to VS-5584 for Mesothelioma**

Image source: NCI

VS-5584, a Verastem PI3K inhibitor and dual inhibitor of mTORC1 and mTORC2, receives orphan drug designation from the FDA for the treatment of mesothelioma. Following preclinical findings that demonstrated synergistic effect from VS-5584 in combination with VS-6063 (defactinib) in mesothelioma, a phase I study is currently underway to assess the combination regimen in patients with relapsed or progressive malignant pleural mesothelioma. The efficacy of VS-5584 is also being evaluated in advanced solid tumors in a phase I dose escalation study.

- **FDA Approves Nivolumab to Treat Metastatic Squamous Non–Small Cell Lung Cancer**

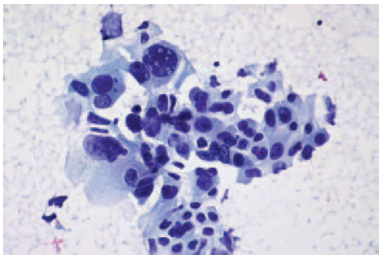


Image credit: Ed Uthman | Flickr | CC BY 2.0 | No modifications

The PD-1 inhibitor nivolumab has been approved by the FDA for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) who have progressed on or after platinum-based chemotherapy. The approval was based on the findings of an open-label, multicenter, multinational randomized trial of 272 patients with the disease, who were treated with nivolumab (n=135) or docetaxel (n=137). Significantly prolonged median overall survival was observed in the nivolumab arm versus the docetaxel arm (9.2 versus 6 months; hazard ratio [HR] = 0.59; *P*=0.00025). Fatigue, shortness of breath, musculoskeletal pain, decreased appetite, cough, nausea and, constipation were among the most common side effects of nivolumab. The most serious side effects were severe immune-mediated side effects involving healthy organs. Nivolumab was previously approved for unresectable or metastatic melanoma, and is being approved for metastatic squamous NSCLC 3 months in advance of the prescription drug user fee goal date.

## NEWS FROM THE IASLC TOBACCO CONTROL COMMITTEE

- **Plain Packaging**

It has been a good month for plain packaging. Ireland passed legislation for mandatory plain packaging for tobacco products on February 26. President Michael D. Higgins signed the legislation on March 10, making Ireland the first European member state to do so. In the UK, MPs have voted in favour of legislation for standardised packing for cigarettes (BBC). The vote on March 11 saw 367 votes for the legislation with 113 votes against it and was reached after the British government first considered standardised packaging in 2011. The vote goes to the House of Lords on Monday March 16, where it is expected to pass and will be introduced in 2016. This brings to three the total number of countries in the world that have made such a move in tobacco control adding the UK and Ireland to Australia. The journal *Addiction* has published research supporting the benefits of plain packaging, summarised in a BBC report as:

Plain packaging reduced unconscious triggers to smoke even in current smokers *(Addiction 2015;110(1):174–82)*

Fewer people made cigarette packs visible in cafes and bars in Australia after the new rules *(Addiction 2014;109(4):653–62)*

The size, shape and opening method do affect brand appeal and increase sales *(Addiction 2013;108(9):1658–68)*

Removing branding draws more attention to health warnings in occasional smokers *(Addiction 2013;108(2):413–19)*

Standardized packs are more effective than larger health warnings *(Addiction 2012;107(6):1159–67)*

http://www.bbc.com/news/health-31839859

http://www.irishtimes.com/news/health/plain-packaging-for-cigarettes-signed-into-law-in-ireland-1.2134138

http://www.bbc.com/news/health-31439211

- **Tobacco Industry Legal Actions**

A major side-effect of successful plain packaging legislation is the tobacco industry reaction. Big Bully, Philip Morris International (PMI) has been engaged in legal action against the Uruguay Government since 2010. Tobacco Tactics, a tobacco control research project at the University of Bath, outlines the legal campaign, an ISDS claim again three Uruguayan measures: (i) an increase in cigarette packet health warnings from 50–80% of the total pack size; (ii) the design of the message in the 80% space; (iii) restriction on one variation of cigarette per brand. On February 20, a tribunal at the Investment Arbitration Reporter tells us that the International Centre for Settlement of Disputes has permitted the WHO/FCTC to submit an *amicus curiae* brief in the PMI v Uruguay case. An *amicus curiae* brief (law.cornell.edu) is a submission in a case by a person or group who is not party to a lawsuit, but who has a strong interest in the matter, in order to influence the court's decision. In this case, according to the Investment Arbitratino Reporter, the tribunal has expressed satisfaction that the WHO and FCTC "bring new perspective, have significant interest and would appear to address matters within scope of dispute". Of course they do you say? It is strange but in the smoke and mirrors world of tobacco industry disputes, such inevitable common sense comes at a struggle sometimes.

http://www.iareporter.com/articles/20150220_1

http://www.tobaccotactics.org/index.php/Philip_Morris_vs_the_Government_of_Uruguay

- **E-Cigarette Updates**

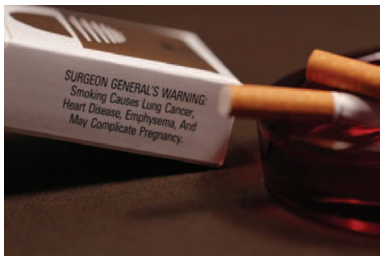



Image source: Debora Cartagena | CDC

Two reports of local anti-tobacco or anti-tobacco-replacement activity tell us about e-cigarette bans. The Oakland Press News reports on a ban on e-cigarette sales to minors. Up to now, under-18s could purchase e-cigarettes. On February the 9, Rochester City Council (Rochester, Michigan) passed a unanimous ruling to prohibit selling and providing e-cigarettes to minors. And a report from The Dallas Morning News from February 11 looks at a proposal in Texas to prohibit the sale of e-cigarettes to minors. The reports quote a recent National Institute on Drug Abuse survey that indicates e-cigarette use in high school students from 8–17%. It is early days in Texas, state senators are reported as considering a "sin tax" (only in Texas??) on vapor products and no plans are yet in place to ban e-cigarette use in public places. And although e-cigarette representatives are reported as supportive of the ban on sales to minors, they expressed concerns about grouping e-cigarettes with tobacco products.

http://www.theoaklandpress.com/general-news/20150216/rochester-joins-communities-with-e-cigarette-ban

http://trailblazersblog.dallasnews.com/2015/02/lawmakers-consider-ban-on-e-cigarette-sales-to-minors.html/

http://www.drugabuse.gov/publications/drugfacts/high-school-youth-trends